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Mechanisms of Improved Exercise Performance under Hyperoxia: On Haldane, Geppert, Zunz, and Eschenbacher Transformations

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We thank Dr. Eschenbacher for his comments [1] on our randomized trial evaluating mechanisms of improved exercise performance under hyperoxia in healthy individuals [2]. Dr. Eschenbacher is concerned about possible errors in our estimations of oxygen uptake ($V'O_2$) based on expiratory minute ventilation ($V'E$) and the inspiratory/expiratory fractions of oxygen and carbon dioxide (FIO_2, FeO_2, and $FeCO_2$) assuming no retention or production of nitrogen (no net N_2 flow) as described by Haldane, an approach commonly termed "Haldane transformation" [3]. From a historical point of view, it is interesting to note that estimation of $V'O_2$ without measuring inspired ventilation and assuming no net N_2 flow has already been proposed by Geppert and Zunz in 1888 [4] (see page 199 of this paper), and the Haldane transformation may therefore as well be termed "Geppert/Zunz transformation".

We used dedicated equipment comprising a gas-mixing device (Altitrainer; SMTEC S.A., Nyon, Switzerland) and a specifically adapted and validated metabolic unit (Ergostik; Geratherm Medical AG, Bad Kissingen, Germany) for measurement of pulmonary gas exchange under conditions of ambient and elevated inspiratory oxygen fractions (FIO_2). In contrast to some standard equipment, the metabolic unit used in our study has been specifically modified to measure FIO_2 rather than to assume a fixed value (for example, FIO_2 0.21 or 0.50). Moreover, the apparatus dead space was carefully measured and appropriately incorporated into the gas exchange computations that included the Haldane transformation as recommended in the guidelines for cardiopulmonary exercise testing [5]. To evaluate the accuracy of the adapted metabolic unit during use with various FIO_2 from 0.21 to 0.50, we have carried out extensive validation studies including measurements with a gas exchange simulator [6]. These experiments revealed a mean bias of +2% in estimated versus predicted $V'O_2$ over a wide range of physiological breathing patterns and simulated $V'O_2$ [7]. The bias of 2% is much smaller than the 7–10% increase in $V'O_2$ observed in our study in healthy subjects at isoloads under hyperoxic versus normoxic conditions. The question is, therefore, how the increased $V'O_2$ with hyperoxia can be explained. As discussed in our paper [2], changes in substrate utilization, alterations in $V'O_2$ kinetics and differences in muscle fiber type recruitment as well as redistribution of blood flow away from working muscles and changes in $V'O_2$ of none-work-performing tissues are potential physiologic explanations. Nevertheless, measurement errors should also be considered when interpreting $V'O_2$. In our experience, admixture of ambient air through leaks in the facemask, mouthpiece or air-conducting tubing of the gas exchange circuit may result in considerable overestimations of $V'O_2$ under hyperoxic conditions. As we used a tightly fitting mouthpiece and checked continuously for absence of air leaks and monitored the gas exchange variables for brisk changes that suggest air leaks, we feel that ambient air admixture is an unlikely explanation for the increase in $V'O_2$ observed in our study.

As Dr. Eschenbacher correctly points out, errors in computation of $V'O_2$ including inadequate assumptions underlying the Haldane transformation, in particular, the absence of net N_2 flow, may also account for overestimation of $V'O_2$. Unfortunately, unlike Geppert and Zunz [4], Dr. Eschenbacher fails to provide adequate evidence to support his theory. Neither the cited white paper of CareFusion [8], a company producing metabolic units incorporating another approach to computation of $V'O_2$ (i.e., the "Eschenbacher transformation"), nor a review by Lang et al. [9] are convincing in this regard, since they do not provide a sound mathematical derivation nor any experimental data to justify the application of their proposed transformation. Moreover, the scientific approach to the derivation of the Eschenbacher transformation seems questionable, since a prerequisite to its design provides plausible values [9]. As the effect of hyperoxia on $V'O_2$ is an unknown quantity, plausibility of estimated values is not a reasonable criterion to select the method for its assessment.

Dr. Eschenbacher cites a study comparing $V'O_2$ measured in 7 ponies during hyperoxia using the Haldane transformation of the Fick equation at the lung based on respiratory gas exchange and the cardiovascular Fick equation based on measurement of cardiac output and the difference in arterial venous oxygen content [10]. $V'O_2$ derived from respiratory gas exchange revealed increased values of $V'O_2$ during hyperoxia (FIO_2 0.60) compared to normoxia (FIO_2 0.21). A similar although statistically nonsignificant trend was observed in $V'O_2$ estimated by the cardiovascular Fick equation. Due to the small sample size, these data were not conclusive. Moreover, we feel that leaks at the mask applied to the pony's nose and mouth and other measurement errors could as likely explain an overestimation of $V'O_2$ derived by respiratory gas exchange measurements as the Haldane transformation. Earlier studies have suggested good agreement between estimates of $V'O_2$ derived with and without the assumption of equal quantities of inspired and expired nitrogen (absence of net N_2 flow) [11].

In conclusion, based on our careful evaluation and validation of $V'O_2$ measurement during hyperoxia and various other studies suggesting an increase in $V'O_2$ under hyperoxia, we have no clear

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evidence that assuming an absence of N_2 flow in calculations of pulmonary gas exchange provides erroneous estimates of $V'O_2$. Nevertheless, we agree with Dr. Eschenbacher that the apparatus setup of gas exchange measurements and calculations of $V'O_2$ should be carefully evaluated, especially during measurements at elevated FIO_2. Independent of the recorded higher $V'O_2$ at isoloads, the main findings of our study, the major increase in endurance during submaximal constant load cycling and the increase in maximal work rate during progressive ramp exercise, are robust.

References

1 Eschenbacher H: Cardiopulmonary exercise testing under hyperoxia: is the Haldane-transformation the correct approach? Respiration 2017;94:71.
2 Ulrich S, Hasler ED, Müller-Mottet S, et al: Mechanisms of improved exercise performance under hyperoxia. Respiration 2017;93:90–98.
3 Haldane JS: Methods of air analysis, ed 2. 1918. https://archive.org/details/cu31924004644484, page 60.
4 Geppert J, Zunz N: Über die Regulation der Atmung. Pflügers Arch 1888;42:189–245.
5 American Thoracic Society; American College of Chest Physicians: ATS/ACCP Statement on cardiopulmonary exercise testing. Am J Respir Crit Care Med 2003;167:211–277.
6 Huszczuk A, Whipp BJ, Wasserman K: A respiratory gas exchange simulator for routine calibration in metabolic studies. Eur Respir J 1990;3:465–468.
7 Hasler ED, Furian M, Saxer S, et al: Validity and reliability of metabolic assessment during cardiopulmonary exercise under ambient air and hyperoxia. Proceedings of the 4th International Issyk-Kul Leh Symposium 2016;2016:38.
8 Eschenbacher H: Haldane and Eschenbacher Transformation 2017.
9 Lang S, Eschenbacher H, Harth V, Preisser AM: Spiroergometrie mit erhöhter Sauerstoffkonzentration – die Haldane Transformation auf dem Prüfstand. Atemwegs- und Lungenkrankheiten 2017;43:86–93.
10 Stanek KA, Nagle FJ, Bisgard GE, Byrnes WC: Effect of hyperoxia on oxygen consumption in exercising ponies. J Appl Physiol Respir Environ Exerc Physiol 1979;46:1115–1118.
11 Wilmore JH, Costill DL: α Adequacy of the Haldane transformation in the computation of exercise VO_2 in man. J Appl Physiol 1973;35:85–89.